Unrelated Bone Marrow Transplantation for β-Thalassemia Patients

The Experience of the Italian Bone Marrow Transplant Group

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ABSTRACT: **Bone marrow transplantation (BMT) remains the only potentially curative treatment for patients with thalassemia major. However, most candidates for BMT do not have a suitable family donor. In order to evaluate whether BMT from an HLA–matched unrelated volunteer donor can offer a probability of cure comparable to that obtained when the donor is a compatible sibling, we carried out a study involving 68 thalassemia patients transplanted in six Italian BMT Centers. Thirty-three males and 35 females (age range, 2–37 years; median age, 15) were transplanted from unrelated volunteer donors, all selected using high-resolution molecular typing of both HLA class I and II loci. Fourteen patients were classified in risk class 1; 16 in risk class 2; and 38 in risk class III of the Pesaro classification system. Nine patients (13%) had either primary or secondary graft failure. Fourteen patients (20%) died from transplant-related causes. Grade II–IV acute graft-versus-host disease (GVHD) developed in 24 cases (40%), and chronic GVHD in 10 cases (18%). Overall survival (OS) in the cohort of 68 patients was 79.3% (CI 67–88%), whereas the Kaplan–Meier estimates of disease-free survival (DFS) with transfusion independence was 65.8% (CI 54–77%). In the group of 30 thalassemic patients in risk classes 1 and 2, the probability of OS and DFS were 96.7%**

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(CI 90–100%) and 80.0% (CI 65–94%), respectively, whereas in the 38 patients in class 3 OS was 65.2% (CI 49–80%) and DFS was 54.5% (CI 38–70%). These data show that when donor selection is based on stringent compatibility criteria, the results of unrelated transplantation in thalassemia patients are comparable to those obtained when the donor is a compatible sibling.

KEYWORDS: unrelated bone marrow transplantation; thalassemia; HLA compatibility criteria

INTRODUCTION

Optimization of erythrocyte transfusion support and regular iron chelation therapy has produced a remarkable improvement in the life expectancy of patients with thalassemia major.[1–3] However, complications related to iron overload cannot be completely avoided by chelation therapy, and compliance with a chronic transfusion regimen is difficult to maintain with advancing age.[3,4] Allogeneic bone marrow transplantation (BMT) from an HLA–identical sibling is currently the only treatment available to cure patients with thalassemia major.[5,6] When the donor is an HLA–identical sibling, the probability of disease-free survival for class 1 and class 2 thalassemia patients is 91% and 84%, respectively.[7–9] The worst results are obtained in the highest-risk category (class 3), particularly in adult patients.[10] The probability of finding an HLA–identical donor within the family is less than 30%. In all other cases, it is necessary to search for a compatible donor among volunteer donors worldwide. Several reports have demonstrated that a more precise characterization of HLA alleles, using high-resolution typing for both HLA class I and class II molecules, can reduce the risk of developing immune-mediated complications and fatal events.[11–13] In view of these considerations, the Italian group for BMT (GITMO) started a pilot study on transplantation from unrelated donors for patients with thalassemia major. The results of this trial have been reported and document the feasibility of this approach.[14]

In this study, we report the outcome of BMT in 68 consecutive thalassemia patients, pertaining to all three risk classes, who were transplanted from an unrelated volunteer donor well matched at the molecular level both for the HLA class I and class II loci.

PATIENTS AND METHODS

Clinical Characteristics of Patients

From June 1992 to September 2004, six Italian BMT Centers transplanted 68 patients with thalassemia major, using an unrelated volunteer as donor. The study received approval from the local institutional review board of each participating center. After detailed explanation of the procedure and its risks, informed consent was obtained from all patients' parents or their legal guardian.

The characteristics of the pretransplant patients are shown in TABLE 1. Thirty-five patients were female and 33 male; age range, 2–37 years (median 15). Prior to transplantation, all patients underwent a complete checkup and were assigned to one of

TABLE 1. Characteristics of patients, donors, and transplants

Median recipient age (years, range)	15 (2–37)
Median donor age (years, range)	35 (20–51)
Gender (male/female)	33/35
HLA donor–recipient compatibility	
HLA-A, -B, -C, -DR, -DQ fully compatible	58 (85%)
HLA-A mismatch	2 (3%)
HLA-B mismatch	2 (3%)
HLA-C mismatch	6 (9%)
HLA-DP mismatch	47 (70%)
Pesaro class at time of BMT	
Class 1	14 (20%)
Class 2	16 (24%)
Class 3	38 (56%)
HCV RNA	
Negative	56 (82%)
Positive	12 (18%)
HCMV serology	
Negative donor/negative recipient	7 (10%)
Positive donor/negative recipient	11 (16%)
Negative donor/positive recipient	18 (26%)
Positive donor/positive recipient	32 (47%)
Donor–recipient sex combinations	
Female donor/male recipient	23 (34%)
Other combination	62 (66%)
Iron chelation	
Regular	26 (38%)
Irregular	42 (62%)
Liver fibrosis	
None	16 (24%)
Mild	10 (14%)
Moderate	31 (46%)
Severe	11 (17%)
Median number of nucleated cells infused (10^8)/kg of recipient weight (range)	3.6 (1.4–11)
Conditioning	
Busulfan/Cyclophosphamide	17 (25%)
Busulfan/Thiotepa/Cyclophosphamide	42 (62%)
Busulfan/Thiotepa/Fludarabine	9 (13%)
GVHD prophylaxis	
Cs-A + MTX	51 (75%)
Cs + MTX + ATG	17 (25%)

NOTE: Oral BU, 14 mg/kg, was administered over 4 days, followed by intravenous CY 50 mg/kg/day for 4 days (total dose 200 mg/kg). TT was given at a dosage of 10 mg/kg, divided into two doses, and added to the same BU-CY combination or to a myeloablative therapy based on the use of oral BU and FLU, 40 mg/m^2/day, for 4 consecutive days.

ABBREVIATIONS: HCMV, human cytomegalovirus; ATG, anti-thymocyte globulin; GVHD, graft-versus-host disease; Cs-A, cyclosporine A; MTX, methotrexate.

three risk classes according to the criteria proposed by Lucarelli *et al.*[15] Risk factors were hepatomegaly, liver biopsy revealing the presence of portal fibrosis, and the quality of pretransplantation iron chelation. The classification of liver iron overload was based on the scheme of Sciot, and portal fibrosis was defined in each patient as mild, moderate, or severe.[15] A four-year-old child did not undergo liver biopsy and was assigned to risk class 1 for lack of the other two risk factors (hepatomegaly and irregular chelation).

Out of 68 patients examined, 14 were assigned to risk class 1, 16 to risk class 2, and 38 to risk class 3. Before allograft, 26 patients (38%) had been compliant with regular iron chelation, which consisted of either subcutaneous infusion of deferroxamine (in the majority of patients) or oral deferiprone. Median serum ferritin level was 828 ng/mL (range, 270–1870) in the 50 class 1 and 2 patients and 1668 ng/mL (range, 1668–4012) in the 38 class 3 patients.

Twelve (18%) out of the 68 patients were hepatitis C virus (HCV)– RNA positive. Details on donor age, donor–recipient human cytomegalovirus (HCMV) serology, as well as donor–recipient gender combinations, are reported in TABLE 1.

HLA Typing and Donor–Recipient Matching

In all donor–recipient pairs, alleles at the HLA-A, -B, -Cw, -DRB1, -DRB3, -DRB4, -DRB5, -DQA1, -DQB1, and -DPB1 loci were identified by polymerase chain reaction–single strand polymorphism (PCR-SSP) and sequence-based typing. Amplification and sequencing of HLA class I and class II genes were performed as previously described.[16–18] Alleles were assigned according to DNA sequences.[19] At the beginning of the study, the protocol required complete identity for all HLA class I (i.e., A, B, and C) and class II loci (i.e., DRB1, DRB3, DRB4, DRB5, DQA1, and DQB1). After the encouraging results obtained with the first transplants and, in view of reports documenting that a single allelic disparity does not unfavorably affect posttransplant outcome,[12] an amendment to the protocol allowed the selection of donors with a single allelic disparity for HLA class I loci. All donor–recipient pairs were matched at the HLA-DRB1, -DRB3, -DRB4, -DRB5, -DQA1, and -DQB1 loci. In 10 donor–recipient pairs, there was a disparity for one HLA class I allele (see TABLE 1 for details). A single or double allelic disparity for HLA-DP was present in 47 of the 68 donor–recipient pairs.

Transplantation Characteristics

In order to prevent any risk related to persistent cytopenia in patients with poor graft function, an autologous rescue of bone marrow cells was harvested and cryopreserved before transplantation for all patients. Data regarding conditioning regimen and number of cells infused are given in TABLE 1. Seventeen patients were transplanted after a preparative regimen, that included busulfan (BU, 14 mg/kg) and cyclophosphamide (CY, 200/120 mg/kg). Because there were concerns about the capability of this preparative regimen to lead to sustained engraftment, the remaining 51 patients were given a modified conditioning regimen, either adding Thiotepa (TT) (10 mg/kg)[14] to the same BU14-CY200/120 combination, or employing a myeloablative therapy based on the use of oral BU14, TT10, and fludarabine (FLU, 160 mg/m^2).

Marrow was infused after 36 and 72 h following the last dose of CY and FLU, respectively. The median bone marrow nucleated cell dose was 3.6×10^8/kg of recipient weight (range, 1.4–11.6). All patients received cyclosporine A (Cs-A), 3 mg/kg/day intravenously from day −2 to day +30, and short-term methotrexate (MTX) for graft-versus-host disease (GVHD) prophylaxis. Cs-A was switched to 6 mg/kg/day orally as soon as oral administration could be tolerated; starting from day +60, the dose was tapered until discontinuation at one year. Seventeen out of the 68 patients were also given anti-thymocyte globulin (ATG, 3.5 mg/kg) on days –3 and –2.[20]

Supportive therapy, as well as prophylaxis and treatment of infections was similar among participating centers. HCMV reactivation was monitored either by expression of the pp56 antigen or by quantitative PCR and treated with either ganciclovir or foscarnet.[21]

Neutrophil and platelet engraftment were defined as the first of three consecutive days with neutrophils $> 0.5 \times 10^9$/L and platelets $> 50 \times 10^9$/L, respectively. Acute and chronic GVHD were graded according to the Seattle criteria.[22,23]

Chimerism was documented by *in situ* Y chromosome hybridization on either bone marrow or blood samples in sex-mismatched donor–recipient pairs, by analysis of variable number of tandem repeat (VNTR) polymorphisms and by microsatellite analysis of bone marrow and/or blood samples in the case of sex-matched pairs.

Data Analysis and Presentation

The reference date of the analysis was November 1, 2004. The median duration of follow-up was 3.4 years (range, 8 months to 12 years). No patient was lost to follow-up. For continuous variables with a symmetric distribution the results are expressed as medians and ranges. Probabilities of survival and survival with transfusion independence were estimated by the product-limit method of Kaplan and Meier and expressed as percentage and 95% confidence intervals (95% CI).[24] For calculation of survival with transfusion independence, data on patients were recorded at the time of death, graft failure, or last follow-up.

RESULTS

From November 1992 to November 2003, 236 consecutive patients with thalassemia major activated a search for an unrelated donor at one of the six BMT centers involved in this study. For 79 patients (33%), a suitable donor was identified. A positive result of donor search ranged from 51% for BMT centers in Sardinia to 28% for the other BMT centers that mainly deal with patients belonging to mixed ethnic groups. The patients who did not find a donor with the required characteristics continued conventional therapy. The median interval between the start of donor search and transplantation was 6 months (range, 2–18 months).

FIGURE 1 shows the Kaplan–Meier probabilities of survival (79.3%, CI 67–88%), event-free survival (65.8%, CI 54–77%), rejection (14.4%, CI 5–23%) and transplant-related mortality (20.7%, CI 11–30%) for the 68 patients studied. The median follow-up of surviving patients was 40 months (range, 8–144 months) .

In 45 patients, the transplant was successful with complete allogeneic reconstitution. The median time for granulocyte recovery was 17 days (range, 7–46 days),

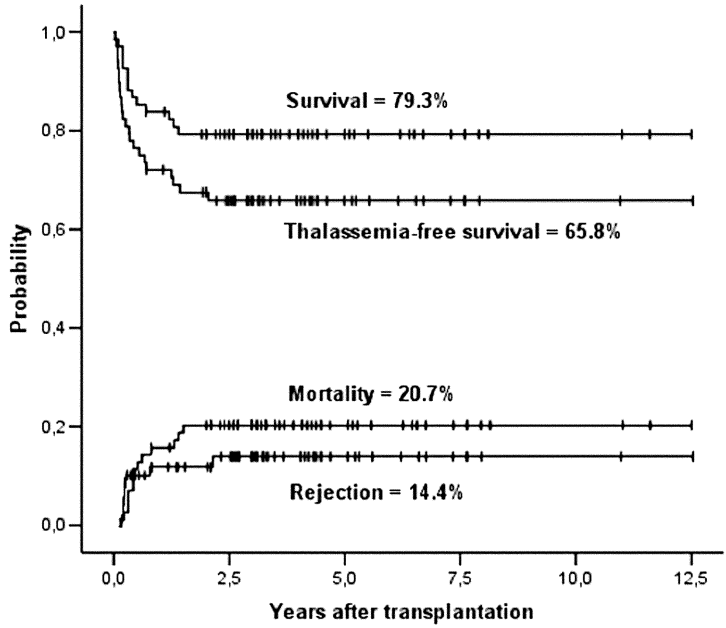

FIGURE 1. Kaplan–Meier probabilities of survival, thalassemia-free survival, and transplant-related mortality and rejection for 68 thalassemia patients relative to all risk classes, transplanted from unrelated donor.

while median time for a self-sustained platelet recovery was 29 days (range, 12–86 days). Sixteen patients died from transplant-related causes. The last death occurred on day +470. In 9 cases, donor marrow was rejected with complete autologous reconstitution and return to the pretransplant clinical status. The last episode of rejection was diagnosed 11 months after the BMT. Twenty-four of 59 evaluable transplanted patients (40%) developed grade II–IV acute GVHD. Ten (17%) of these patients had grade III–IV GVHD. Among the 56 evaluable cases, 10 (18%) developed chronic GVHD, limited in 5 cases and extended in the other 5.

The analysis of the data confirms that transplant outcome is strongly influenced by risk class. In fact, if we consider the cohort of 38 patients in the high-risk class (class 3), the results obtained are less satisfactory. In this category of patients, the mean age was 19 years (range, 6–37 years), none of them had received regular iron-chelation therapy and all had high-grade portal fibrosis (moderate in 71% of patients and severe in 29%). In this cohort of patients (FIG. 2), the Kaplan–Meier estimate of survival and the probability of disease-free survival was 65.2% (CI 49–80%) and 54.5% (CI 38–70%), respectively, and the probability of transplant-related mortality and rejection was 34.8% (CI 19–50%) and 10.8% (CI 8–28%). Grade II–IV acute GVHD developed in 18 cases (56%). Among the 26 evaluable patients, 7 (27%) developed chronic GVHD.

In contrast, the results obtained for the group of 30 thalassemic patients in the low-risk classes 1 and 2, with a mean age of 8 years (range, 2–17 years) and charac-

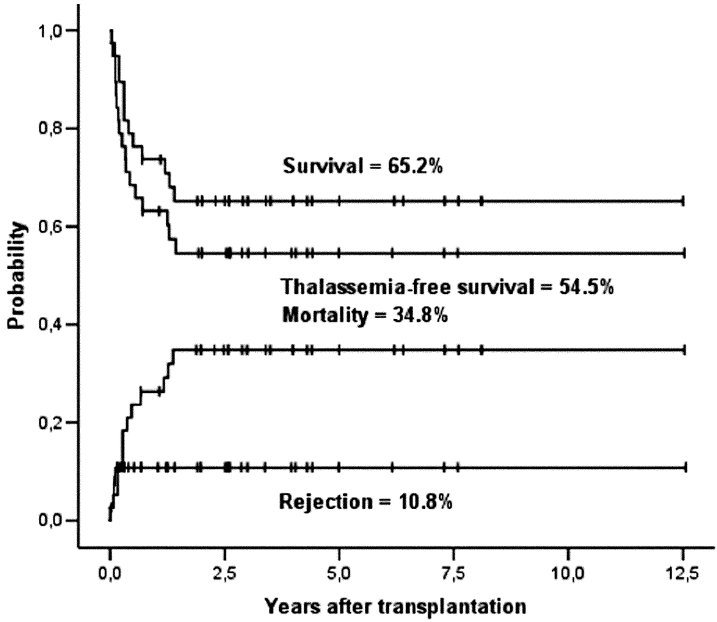

FIGURE 2. Kaplan–Meier probabilities of survival, thalassemia-free survival, and transplant-related mortality and rejection for 38 class 3 thalassemia patients, transplanted from unrelated donor.

terized by a good iron chelation regimen and a low grade of portal fibrosis, can be considered extremely positive. FIGURE 3 shows Kaplan–Meier probabilities of survival (96.7%, CI 90–100%), event-free survival (80.0%, CI 65–94%), rejection (20.0%, CI 3–30%), and no rejection mortality (3.3%, CI 3–30%) for the 30 class 1 and 2 patients. Eight out of the 27 patients (29%) who engrafted experienced grade II–IV acute GVHD. Chronic GVHD developed in 3 (11%) of the 26 patients at risk.

DISCUSSION

The majority of the patients with thalassemia do not have an HLA donor within the family. For this reason, in the last 10 years, BMT centers engaged in the treatment of hemoglobinopathies have been exploring the possibility of transplantation utilizing alternative donors. In view of these considerations, GITMO started a pilot study on transplantation from unrelated donors for patients with thalassemia major. The results of this trial have been reported and document the feasibility of this approach.[14]

In our series of 68 patients, rejection and transplant-related mortality rates were 11% and 18%, respectively. Seventy-one percent of patients are alive, transfusion independent, with sustained engraftment of donor hematopoiesis, thus leading to a projected free survival of 65.8% (FIG. 1).

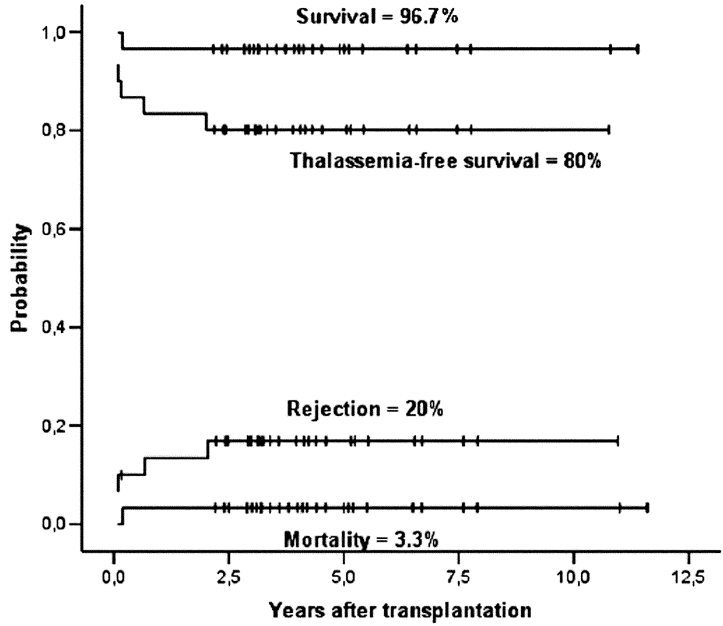

FIGURE 3. Kaplan–Meier probabilities of survival, thalassemia-free survival, and transplant-related mortality and rejection for 30 class 1 and 2 thalassemia patients, transplanted from unrelated donor.

Thirteen deaths were observed among the 38 class 3 patients (34%). In class 3 patients, the risk of mortality is high even when the donor is an HLA–identical sibling.[10,25,26] In this cohort of 38 class 3 patients, a higher incidence of deaths was observed in the group of patients conditioned with the protocol, including TT (9/22 = 41%) compared to patients conditioned with BU-CY alone (4/16 = 25%). Although this difference was not significant, a conditioning regimen with three drugs (BU-TT-CY) is likely to be too toxic for this category of patients. Therefore, the protocol based on BU-CY alone should be the treatment of choice in this category of patients. A recent report on a group of 33 class 3 thalassemia patients, aged less than 17 years and transplanted from HLA–identical siblings, has demonstrated the efficacy of a new and less aggressive conditioning regimen.[27] It can be postulated that this innovative approach may contribute to the successful outcome of unrelated BMT in adult class 3 thalassemia patients.

The outcome of unrelated BMT in our cohort of 30 class 1 and 2 patients was similar to that reported in the literature[28] for the same risk classes. In this group of patients, the Kaplan–Meier estimate of disease-free survival after the first transplant was 80% (FIG. 3). One patient died (3%) and 5 (17%) experienced rejection. In this category of patients, the use of a conditioning regimen containing TT and FLU seems to enhance sustained engraftment of donor cells. In fact, 1 of 2 patients (50%) conditioned with BU-CY did not have sustained engraftment, while the incidence of graft failure in the group conditioned with the regimen including TT and/or FLU was 14% (4/28).

The relatively low incidence of acute and chronic GVHD (40% and 18%, respectively) in the total group of patients confirms that a careful immunogenetic selection of donor–recipient pairs has an important role in reducing the incidence of this complication. A single allelic disparity at HLA class I loci did not significantly correlate with GVHD or rejection. Conversely, in the group of DPB1–mismatch recipients, there was a significant increase of immunologic complications (data not shown).

In conclusion, BMT from unrelated donors, selected by use of high-resolution typing for both HLA class I and class II molecules, may offer similar results to those obtained using HLA–identical family donors. It may therefore be an acceptable therapeutic approach in thalassemia, at least for patients who are not fully compliant with conventional treatment and do not yet show severe complications of iron overload.

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